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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,215	03/27/2001	Scott A. Waldman	08321-0166 US	2195

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EXAMINER	
CALAMITA, HEATHER	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/820,215	WALDMAN ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-11,13-15 and 37-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-11,13-15 and 37-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/05/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Amendments of September 25, 2006, have been received and entered in full. Claims 1, 4, 6-11, 13-15 and 37-47 are pending and under examination. Any objections and rejections not reiterated below are hereby withdrawn.

Written Description

2. Claims 1, 4, 6-11, 13-15 and 37-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to methods of detecting the presence of *a disseminated epithelial cell marker* in a sample comprising the steps of

a) eliminating CD34+ cells from the sample; and

b) *detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen.* (emphasis added).

Thus, the claims are drawn to methods of detecting "disseminated epithelial cell markers", wherein after the elimination of CD34+ cells, "mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen" is detected. Accordingly, the claims are drawn to detecting the genus of "mRNA that encodes a disseminated epithelial marker, wherein the marker is differentiation specific".

This genus comprises the class of compounds (mRNAs) that share a function (encoding a disseminated epithelial cell marker, wherein the marker is a differentiation-specific antigen). However, the specification does not specify a common structure of this class of mRNAs. That is, while the members of the genus encompassed by the claims (e.g., the mRNA encoding a disseminated epithelial

cell marker, wherein the marker is a differentiation-specific antigen), share a function, they do not share a structure that is similar. Each mRNA encompassed by the genus will have different structure, absent any disclosed structural similarities provided by the specification. That is, even assuming, the mRNAs encompassed by the genus are functionally similar, they are not structurally similar, and therefore, the functional description of the mRNAs does not provide adequate written description to the plurality of other structurally distinct mRNAs that are encompassed by the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed* (See page 1117)." (emphasis added)

Additionally, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification teaches eight epithelial cell markers (see page 10, lines 7-10), and asserts these epithelial cell markers "can be" used as disseminated markers (see page 12, lines 10-27). However, these markers are not structurally related, nor do they share any common sequences, and

therefore, these eight species are not considered to be a representative number of species. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., similar structural motifs, sequence similarity, etc.). In the instant case, no such identifying characteristics have been provided for any of the claimed nucleic acids. Furthermore, it is noted that the specification does not describe which mRNA are specific for which "differentiation-specific antigen". In other words, the specification does not describe which mRNAs are specific for a particular tissue-specific marker.

Accordingly, because the specification does make clear that Applicants were in possession of the genus of mRNAs that encode disseminated epithelial cell markers, wherein the cell markers are differentiation-specific antigens, at the time the application was filed, the claims lack adequate written description.

Applicant's attention is also drawn to the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1st Paragraph, Written Description Requirement" (published in Federal Register/Vol. 66, No. 4/Friday, January 5, 2001/Notices; p. 1099-1111).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6-11, 13 and 37-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o et al. (USPN 5,962,237, 1999), in view of Elliot (USPN 5,885,574, 1999).

With regard to claim 1, Ts'o teach a method of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of

a) eliminating CD34+ cells from the sample (see cols. 18-19, example 2, where prostate cancer cells were added into whole blood cells and the cancer cells were isolated and the white cells, i.e. CD34+ cells are a species of white blood cells are removed from the cancer cells).

b) detecting the presence of mRNA that encodes the marker; wherein the marker is a differentiation specific antigen; wherein the detection of said mRNA indicates the presence of a disseminated epithelial cell marker (see col. 20, example 7 lines 62-65, where FISH was used to detect PSA and PSMA mRNA).

With regard to claim 3, Ts'o teach the tissue is prostrate (see col. 6 line 1).

With regard to claim 4, Ts'o teach a method of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of

a) eliminating CD34+ cells from the sample to reduce false positives (see cols. 18-19, example 2, where prostrate cancer cells were added into whole blood cells and the cancer cells were isolated and the white cells, i.e. CD34+ cells are a species of white blood cells are removed from the cancer cells. Ts'o is silent as to the reduction of false positives, however as Ts'o teaches the removal of white cells and CD34+ cells are a species of white cells it necessarily follows when the CD34+ cells are removed false positives will necessarily be reduced)

b) detecting the presence of mRNA that encodes the marker; wherein the marker is a differentiation specific antigen; wherein the disseminated epithelial cell marker is Prostate specific antigen or prostate specific membrane antigen wherein the detection of said mRNA indicates the presence of a disseminated epithelial cell marker (see col. 20, example 7 lines 62-65, where FISH was used to detect PSA and PSMA mRNA).

With regard to claim 7, Ts'o teach the sample is tissue or bodily fluid (see col. 5 lines 48-51, where Ts'o teaches blood and tissue samples).

With regard to claim 8, Ts'o teach the sample is blood or lymph tissue (see col. 5 lines 48-51).

With regard to claims 9 and 42, Ts'o teach the mRNA is detected by a polymerase chain reaction-based method (see col. 13 lines 50-55).

With regard to claim 10, 11, 43 and 44, Ts'o teach the mRNA is detected by RT-PCR (see col. 17 lines 47-54).

With regard to claim 13, 40 and 45, Ts'o teach the marker is PSA and PSM (see col. 16 lines 62-65).

With regard to claim 37, Ts'o teach the sample is mononuclear cells isolated from blood (see col. 16 lines 58-59, where lymphocytes are a subset of mononuclear cells).

With regard to claim 38, Ts'o teach the disseminated epithelial cell marker is a tissue-specific marker (see col. 20, example 7 lines 62-65, where PSA and PSMA are tissue specific markers).

With regard to claim 39, Ts'o teach the tissue is prostrate (see col. 6 line 1).

With regard to claim 1, Ts'o teaches eliminating a variety of white cells using antibodies attached to immunoaffinity beads, however Ts'o does not teach using an anti-CD34 antibody based affinity process.

With regard to claims 6 and 41, Ts'o again teaches eliminating a variety of white cells using antibodies attached to immunoaffinity beads, however Ts'o does not specify that this method of using beads and antibodies is a method of column chromatography.

Elliot teaches the elimination of CD34+ using a CD34 Progenitor Cell Isolation Kit (QBend/10) made by Miltenyi Biotech GmbH, wherein "cells are tagged with an anti CD34 monoclonal antibody they were then bound to magnetic microspheres according to protocol. The tagged cells were next passed through pre-filled MiniMacs separation columns, the columns were washed and the CD34+ cells were then eluted from the column." (col. 22, lines 34-41, where Elliot teaches this column chromatography protocol results in higher purity isolation of the CD34+ cells).

Accordingly, in view of the teachings of Elliot, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ts'o so as to have used column chromatography and anti-CD34 antibodies for eliminating specific white cells. One of ordinary skill in the art would have been motivated to modify the method of Ts'o in order to have achieved the benefit of providing a more effective means of isolating and diluting out specific white cells to ensure a better isolation and analysis of the rare tumor cells.

4. Claims 14-15 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o et al. (USPN 5,962,237, 1999) and Elliot (USPN 5,885,574, 1999) as applied to claims 1 and 37 above and in further view of Waldman et al. (Cancer Epidemiology, Biomarkers & Prevention, 1998).

The teachings of Ts'o and Elliot are presented above. The references teach methods of detecting epithelial cell markers, comprising eliminating CD34+ cells using an anti-CD34 antibody based affinity process and detecting mRNA encoding said cell marker, wherein said cell marker is a differentiation-specific antigen. The references teach the rare cells can be epithelial cells (i.e., comprising epithelial cell markers, such as PSA and PSM, see col. 13, lines 56-67, for example), but do not teach all the limitations

of claims 14, 15, 46 and 47, specifically, wherein the epithelial cell marker is GC-C and a marker for metastatic colon cancer.

Waldman teaches the detection of GC-C, which is an epithelial cell marker for colorectal cancer, and can be used in diagnosing colorectal cancer, one of the most common forms of cancer (see abstract, page 505, 1st column and pages 510 and 512).

Accordingly, in view of the teachings of Waldman, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ts'o and Elliot so as to have detected the epithelial marker, GC-C. One of ordinary skill in the art would have been motivated to modify the method of Ts'o and Elliot in order to have achieved the benefit of providing a means of diagnosing colorectal cancer, which is one of the most common forms of cancer.

Response to Arguments

5. Applicants' arguments filed September 25, 2006, have been fully considered but they are not persuasive.

With respect to the written description rejections of claims 1, 4, 6-11, 13-15 and 37-47, applicants argue the disclosure describes a representative number (26) species of the genus. However, it is again noted applicants fail to describe a representative number of species for this genus. The genus is comprised of about 20,000 known human genes of which an unknown number are epithelial cell markers. Applicants have adequately described only 26, or less than 0.2 %. Less than 0.2 % is not a representative number of species for this genus, therefore the written description rejection hereby maintained.

With respect to the 102 (b) rejections Applicants' arguments have been considered but are moot in view of the new ground(s) of rejection.

With respect to the 103 (a) rejections over Ts'o and Elliot, Applicants argue Ts'o neither teaches nor suggests specifically eliminating CD 34 cells and there is no motivation to do so. This argument is

not persuasive because as outlined in the rejection Ts'o removes white cells using antibodies to enrich for cancer cells and Elliot teaches the removal of a specific kind of white cell (namely CD34) using an antibody specific for CD 34 cells. As stated in the rejection above one of ordinary skill in the art would be motivated to use the affinity method disclosed by Elliot with the method of enriching a sample for cancer cells to have the benefit of a more effective means of isolating and diluting out specific white cells to ensure a better isolation and analysis of the rare tumor cells.

Applicants argue Ts'o teaches removal of other subpopulations not CD34 cells. It appears Applicants are arguing this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e., a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that populations of white cells can be removed with immunoaffinity beads (antibodies attached to beads) by Ts'o. There is further evidence as shown by Elliot that specifically, anti-CD34 antibodies are useful in the removal of CD 34 cells from a sample. This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention

> or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of immunoaffinity beads, anti-CD 34 antibodies and the removal of white cells from samples. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of anti-CD 34 antibodies for the removal of CD 34 cells from a sample as discussed in the rejection and as taught by Ts'o and Elliot.

Additionally, Applicants argue Ts'o teaches away from the elimination of CD 34 cells by antibody based affinity methods. This argument is not persuasive because Applicants do not substantiate this argument by indicating which of Tso's teachings constitute a teaching away.

Finally Applicants argue the combined teachings of Ts'o and Elliot teaches or suggests the unexpected elimination of false positives. This argument is not persuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

With regard to the 103 (a) rejections over Ts'o and Waldman, Applicants' arguments have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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